Pharmacology Biochemistry & Behavior, Vol. 6, pp. 359–361.

BRIEF COMMUNICATION

Caffeine Potentiation of Amphetamine: Implications for Hyperkinesis Therapy

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(Received 9 December 1976)

SCHECHTER, M. D. *Caffeine potentiation of amphetamine: implications for hyperkinesis therapy*. PHARMAC. BIOCHEM. BEHAV. 6(3) 359–361, 1977. – Neither 0.05 mg/kg d-amphetamine nor 15 mg/kg caffeine alone produce amphetamine-like responding in rats trained in two-lever operant chambers to discriminate 0.8 mg/kg d-amphetamine from saline. The co-administration of the two drug doses produced responding similar to the 0.8 mg/kg d-amphetamine dose. A suggestion for the mechanism of action and a regimen of administration for caffeine in hyperkinetic children are discussed.

Amphetamine Caffeine Dopamine Drug-induced stimulus control Haloperidol Hyperkinesia

IN children with the minimal brain dysfunction (MBD) syndrome and subsequent hyperkinetic impulse disorder, psychostimulants, such as d-amphetamine, d, l-amphetamine, methylphenidate and pemoline, are effective in increasing attention span, in lessening mood swings and perseverance, and in diminishing hyperactivity [2,3]. Unfortunately, all of these (Schedule 2) drugs have been reported to produce side effects that include: loss of appetite and weight, nervousness, insomnia or restless sleep patterns, abdominal complaints, and after chronic use, they have a potential for growth deprivation [11]. This has led to a growing concern regarding the use of the psychostimulants, and has made it desirable to find a drug with at least equal therapeutic efficacy but with less marked side effects. A pilot study suggested that caffeine, in the form of coffee, may have a place in the therapeutic management of hyperkinetic children [13]. Subsequent well-controlled clinical investigations, however, indicated that caffeine, by itself, is not effective as a substitute for the psychostimulants in the treatment of MBD [5,7].

The fact that many hyperkinetic children respond dramatically to treatment with drugs that stimulate the central nervous system by interacting with monoamine neurotransmitter mechanisms has led to the hypothesis that at least one subgroup of children with MBD may have a functionally under-active monoamine system in their brain. Indeed, Meyerhoff and Snyder [10] have proposed that the beneficial effects of amphetamine are due to the ability of this drug to increase the availability of dopamine to its receptor sites in the brain. Drug-induced control of discriminative behavior in rats with d-amphetamine has been shown to be mediated by dopaminergic systems in the central nervous system [11], and this behavioral technique has been employed to test various direct- and indirect-acting dopaminergic drugs [6]. In an effort to investigate whether caffeine might be substituted for amphetamine in the therapy of the hyperkinetic syndrome, amphetamine-induced stimulus control in rats was used as a model for dopaminergic receptor stimulation and the effect of caffeine on this behavior was determined.

MATERIALS AND METHOD

The procedure used for the present experiment has been described in detail elsewhere [6]. In brief, the apparatus consisted of two standard animal test environments (BRS/LVE), fitted with two levers, a food pellet delivery system, and was programmed by solid-state logic modules. Eight male Sprague-Dawley rats were maintained at 80 ± 5% of their expected free-feeding weights and were trained to lever press for food (45 mg Noyes food pellets) on either of the two levers. Fifteen min after intraperitoneal (IP) injection of 0.8 mg/kg d-amphetamine sulfate (as base), the rats were required to press one of the levers (amphetamine-correct) in order to receive reinforcement; upon administration of an equal volume of saline (0.9% sodium chloride), they were required to press the other lever (saline-correct). The schedule of reinforcement employed was an extinction-variable interval 15 sec schedule in which no lever presses were reinforced during the initial 2.5 min of each session. This was followed by food delivery for every lever-press made on the correct lever on a variable interval averaging 15 sec for the remaining 12.5 min of each session. Every week, each rat was run in daily 15 min

sessions on six consecutive days with a double alternation schedule of administration. The 2.5 min extinction period of each session was used to ascertain discriminative performance. Criteria performance was established as the achievement of 80% correct responses with both d-amphetamine and saline.

Criterion performance was attained after 10 sessions with each condition and d-amphetamine and saline maintenance sessions were continued in order to assure reliable performance. Each dose response and test drug session was preceded by one saline and one d-amphetamine training session. On test sessions, the rats were administered (IP) lower doses of amphetamine than the training dose of 0.8 mg/kg and responding in the 2.5 min extinction period was recorded; there was no further training. The ED50 was ascertained to be 0.13 mg/kg. Subsequently, a lower dose of d-amphetamine, 0.05 mg/kg, was administered five minutes after the administration (IP) of 15 mg/kg caffeine during extinction test sessions in order to investigate the effect of caffeine upon a dose of d-amphetamine that produced low levels of discriminative responding. Likewise, 15 mg/kg caffeine was tested alone and 0.25 mg/kg haloperidol (Haldol) was administered (IP) 30 min before the combined treatment. All test treatments were given to each of the 8 trained animals on two occasions in a random order.

TABLE 1

PERCENT RESPONDING ON *d*-AMPHETAMINE LEVER FOLLOWING MAINTENANCE AND TEST DRUG SESSIONS

Treatment	Dose (mg/kg)	Percent Amphetamine Lever Choice (±SE)
I. *d*-Amphetamine*	0.8	92.2 ± 2.4
Saline	—	12.6 ± 2.9
d-Amphetamine	0.4	82.4 ± 7.0
	0.2	63.5 ± 4.8
	0.1	46.6 ± 11.0
II. *d*-Amphetamine	0.8	90.9 ± 2.2
Saline	—	7.4 ± 2.3
d-Amphetamine	0.05	24.4 ± 4.4§
Caffeine	15.0	43.7 ± 7.9§
Caffeine	15.0	
+		86.6 ± 3.3
d-Amphetamine	0.05	
Haloperidol‡	0.25	
+		
Caffeine	15.0	43.7 ± 5.2§
+		
d-Amphetamine	0.05	

*d-Amphetamine (0.8 mg/kg) and saline maintenance sessions interspersed amongst test sessions. Five IP administrations of each treatment to each of eight rats fifteen min before testing in extinction. All test sessions consisted of two sessions in each animal in random order.

‡Haloperidol was administered IP 30 min prior to *d*-Amphetamine and caffeine. Testing, in extinction, fifteen min after last injection.

§Probability of test drug choice responses being different from both *d*-amphetamine or saline response due to chance: $p<0.01$ Mann-Whitney U test.

RESULTS

Percent responding on the d-amphetamine lever following 0.1, 0.2, 0.4 and 0.8 mg/kg d-amphetamine, saline and test drugs are presented in Table 1. The values for d-amphetamine and saline represent the percent of total responses on the d-amphetamine-correct lever during the extinction period of maintenance sessions interspersed among dose-response and novel drug tests. Part 1 indicates that if rats first learn a drug versus saline discrimination with a specific training dose and then receive test sessions with lower doses of the same drug, the number of drug-appropriate responses decreases in an orderly fashion as the test dose is lowered. A dose of 0.05 mg/kg d-amphetamine produced 24.4% responses on the amphetamine lever, or to view it differently, 75.6% responding on the saline-appropriate lever (Part 2). Caffeine administered alone produced 43.7% responding on the d-amphetamine lever. The combination of d-amphetamine and caffeine, however, produced 86.6% responding on the amphetamine lever which is not significantly different from responses after the training dose of d-amphetamine. Haloperidol, 0.25 mg/kg, administered (IP) 30 min prior to the two drugs decreased responding on the d-amphetamine lever to 43.7%.

DISCUSSION

It has been suggested that the hyperkinetic impulse disorder, or MBD, in children may be caused by a deficit in dopaminergic post-synaptic stimulation that interferes with interneuronal transmission. This, in turn, alters the function of the reticular activating system in the diencephalon that helps to maintain cortical dominance over diencephalic-limbic lobe structures [15]. Drugs such as amphetamine and methylphenidate are presumed to be effective in the treatment of MBD by increasing the release of dopamine. Caffeine has been reported to potentiate circling behavior [4] and hypermotility [1,14] induced by levodopa in rats and to potentiate amphetamine- and apomorphine-induced stereotypic behavior in guinea pigs [9]. Although these animal behaviors are used as models for dopaminergic stimulation, caffeine by itself does not seem to be effective in the treatment of MBD in children [5,7].

Drug-induced stimulus control of discriminative behavior with d-amphetamine appears to be a sensitive test for dopaminergic mechanisms in the rat brain [6,11]. In the present study, the administration of 15 mg/kg caffeine or 0.05 mg/kg d-amphetamine produced low levels of drug-induced discriminative responding when compared to those produced by 0.8 mg/kg d-amphetamine (Table 1, Part 2). However, the co-administration of the two drugs at these doses was observed to produce responding similar to that seen after the higher dose of d-amphetamine. The observation that haloperidol, a specific dopaminergic receptor blocker, abolishes the response to the two drugs administered simultaneously indicates that the stimulus effect of the d-amphetamine component is dopaminergically mediated.

An explanation for this effect, i.e., the mechanism of action by which caffeine potentiates amphetamine, may be found in the in vitro work of Kebabian *et al.* [8] in which caffeine, a potent inhibitor of phosphodiesterase that cleaves cyclic 3',5'-adenosine monophosphate (cAMP), increases the level of adenyl cyclase. It has been suggested that adenyl cyclase may be the receptor for dopamine in

mammalian brain. Thus, supersensitizing of these receptors to dopamine may occur and produce a functional increase to any presynaptic dopamine released by small doses of d-amphetamine.

The results of this investigation suggest that caffeine should be subjected to clinical trials, not as a substitute for psychostimulants in the therapy of MBD, but in conjunction with reduced dosages of amphetamine. If caffeine co-administered with a smaller dose of amphetamine produces adequate control of MBD the side effects of the more potent psychostimulant may be avoided.

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